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ORIGINAL RESEARCH

Neural correlates of emotional valence processing in Parkinson's disease: dysfunction in the subcortex

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Abstract Parkinson's disease (PD) is frequently accompanied by cognitive and neuropsychiatric symptoms including impairments in affective processing. Despite this, mechanisms underlying vulnerability to deficits in affective processing remain unclear. In this study, we utilized functional Magnetic Resonance Imaging (fMRI) and an Affective Go-NoGo paradigm, to examine the neural correlates of emotional valence processing in PD. Results suggest that PD is associated with aberrant processing of emotional valence in subcortical limbic structures. Specifically, we found significant group-by-valence interactions in the ventral striatum and amygdala in response to words of differing emotional valence. Our findings contribute to a broader understanding of affective processing in PD and may provide insights into the mechanisms underlying vulnerability to mood disorders in PD.

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Keywords Amygdala · Dopamine · Emotion · Parkinson's disease · Ventral striatum

Abbreviations

AGNG	Affective Go-NoGo
PD	Parkinson's disease
VTA	Ventral Tegmental Area

Introduction

Although predominantly recognised as a motor disorder, Parkinson's disease (PD) is frequently accompanied by cognitive and neuropsychiatric symptoms (Chaudhuri and Schapira 2009). Recent neuropsychological work has revealed that individuals with PD demonstrate a range of deficits in affective processing and emotional regulation including; altered subjective emotional experience (Wieser et al. 2006; Hillier et al. 2007), impaired physiological arousal (Bowers et al. 2006), and deficits in the recognition and production of emotional prosody and facial expression (Simons et al. 2004; Mobes et al. 2008; Gray and Tickle-Degnen 2010). Despite these insights, the neurocognitive mechanisms underlying deficits in emotional processing in PD remain unclear. By combining in vivo functional imaging with an emotional processing task, this study seeks to elucidate the neural substrates unpinning emotional processing deficits in PD.

PD is characterized by degeneration of select neuronal cell groups in the midbrain and brainstem (Braak et al. 2003). Ascending mesoencephalic dopaminergic projections

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are particularly vulnerable to neurodegeneration in PD (Braak et al. 2003), resulting in dopaminergic denervation of subcortical structures including the basal ganglia and amygdala (Remy et al. 2005; Bruck et al. 2006), as well as neocortical regions (Scatton et al. 1982). Loss of ascending dopaminergic input to the subcortex is believed to underlie pathological activity within cortico-striatal-thalamic macrocircuits (Kwak et al. 2010; Hacker et al. 2012; Dubbelink et al. 2013; Yang et al. 2016), and has been linked to motor impairments in PD (Brown 2007). More recently, it has been proposed that dopamine cell loss may also contribute to affective processing deficits in PD by depleting frontal-subcortical and amygdala circuitry of dopamine (Peron et al. 2012), however direct empirical evidence supporting this hypothesis is currently limited and indirect.

In this fMRI study, we examined the neural substrates underlying inhibitory processing of affective *valence* in individuals with PD and age-matched healthy controls. To our knowledge, this is the first imaging study to specifically examine how emotional valence is processed in PD. To achieve this, we utilized the Affective Go-NoGo (AGNG) task, an inhibitory control paradigm that requires participants to respond to words of a target valence (positive or negative), while simultaneously inhibiting responses to words of competing valence (Murphy et al. 1999). The AGNG paradigm has previously enabled insights into the neural correlates of affective processing in healthy individuals (Elliott et al. 2000; Roiser et al. 2008), as well as abnormal emotional processing in Major Depressive Disorder (Murphy et al. 1999; Elliott et al. 2002a; Erickson et al. 2005; Roiser et al. 2009) and Bipolar Disorder (Murphy et al. 1999; Elliott et al. 2004). Furthermore, recent longitudinal work has shown that the AGNG paradigm shows promise in identifying trait vulnerability to future depressive disorders during adolescence (Kilford et al. 2015).

We hypothesized that during emotional word processing, individuals with PD would exhibit differential patterns of neural activation in the ventral striatum, caudate and amygdala, compared to healthy age-matched controls. Our rationale for predicting abnormal activity in these subcortical regions was threefold: (i) each of these subcortical regions have been implicated in emotional processing in healthy subjects (LeDoux 2000; Phillips et al. 2003; Postuma and Dagher 2006; Arsalidou et al. 2013); (ii) each region is modulated by direct innervation from dopaminergic midbrain nuclei (Moore 2003); and (iii) these regions have each been implicated in the pathophysiology of mood disorders characterized by impairments in emotional processing (Phillips et al. 2003; Drevets et al. 2008; Korgaonkar et al. 2014).

Experimental procedure

Participants

Thirteen patients with mild-to-moderate idiopathic PD (United Kingdom Parkinson's Disease Society Brain Bank criteria) were recruited via the Brain and Mind Research Institute, Parkinson's Disease Research Clinic, The University of Sydney. Inclusion criteria were (i) Hoehn and Yahr Scale 1–2.5; (ii) aged 50–85; (iii) English speaking; (iv) non-demented (Montreal Cognitive Assessment Scale ≥26) (Dalrymple-Alford et al. 2010)); not currently depressed (Beck's Depression Inventory ≥15) (Visser et al. 2006) and (v) no contraindications to magnetic resonance imaging. Motor severity was assessed in the clinically defined 'on' state using the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Goetz et al. 2007). In addition, patients with PD also completed the Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire (QUIP) (Weintraub et al. 2009). Note that, although subjects with current depression were excluded from this study, two of the included thirteen PD patients had a past history of a depressive disorder. Both of these patients had a history of a single six-month episode of Major Depressive Disorder prior to diagnosis with PD. Since this prior episode, one of these patients had been on antidepressant medication to prevent mood relapse, however the other was not on antidepressant medication. See Table 1 for demographic and clinical variables.

The current medication treatments for the PD subjects were as follows: one patient was untreated, one patient was taking dopamine agonist monotherapy, four were taking levodopa monotherapy, five were taking a combination of levodopa and dopamine agonist therapy, one was taking a combination of levodopa, dopamine agonist and monoamine oxidase inhibitor and one was taking a combination of levodopa, dopamine agonist and catechol-O-methyl transferase inhibitor. In addition to their PD treatment, two patients were on nocturnal benzodiazepine and one patient was on antidepressant medication to aid sleep. Finally, one patient was on antidepressant medication to prevent mood relapse (see above). Levodopa equivalent dose (LED) was calculated according to Tomlinson et al. (2010) (see Table 1).

In addition, twelve age-matched healthy controls were recruited via the Brain and Mind Research Institute, The University of Sydney. Inclusion criteria were (i) no history of psychiatric or neurological disorder(s), (ii) aged 50 to 85; (iii) English speaking; (iv) non-demented (Montreal Cognitive Assessment Scale ≥26) and (v) no contraindications to magnetic resonance imaging. The University of Sydney Human Research and Ethics Committee approved the study and written informed consent was obtained from each participant.

All participants completed the Beck Depression Inventory II (Beck et al. 1996), letter fluency tests, Spielberger Trait

Table 1 Demographics and clinical variables

	Mean (SD)		*p* value
	PD	HC	
N	13	12	-
Male/Female[#]	11/2	3/9	0.003
Age	66.31 (5.9)	66.50 (6.9)	0.941
MoCA[a]	28.23 (1.4)	28.83 (1.5)	0.225
BDI-II	7.08 (3.5)	6.08 (4.5)	0.540
Education (yrs)	15.46 (2.8)	15.58 (2.6)	0.912
STAI	28.77 (4.9)	27.58 (4.0)	0.955
SSAI	31.69 (5.9)	31.83 (6.3)	0.516
AS	12.23 (5.4)	11.58 (6.3)	0.785
NART	114.23 (12.4)	117.75 (6.7)	0.394
BIS-11	8.71 (2.5)	10.29 (3.0)	0.212
B&L-MS Factor 1	36.90 (10.0)	30.22 (7.6)	0.074
B&L-MS Factor 2	30.28 (11.6)	23.32 (6.5)	0.081
B&L-MS Factor 3	36.92 (14.6)	26.38 (1.2)	0.056
Verbal fluency age-adjusted Z-score (letter)	0.41 (1.3)	0.49 (1.3)	0.894
Verbal fluency age-adjusted Z-score (category)	0.35 (1.1)	0.48 (0.9)	0.734
Disease Duration (years)	7.31 (2.2)	-	-
DDE	520.73 (288.7)	-	-
UPDRS-III	19.62 (8.6)	-	-

[a] Mann-Whitney U test used to compare groups where data was not normally distributed according to the Shapiro-Wilk test for normality. [#] Chi square test was used to compare gender balance. *Abbreviations.* BIS-II, Barret's Impulsivity Scale-11; BDI-II, Becks's Depression Inventory-II; B&L-MS, Bond and Lader Mood Scale; DDE, Dopamine Dose Equivalent; HC, Healthy Controls; MoCA, Montreal Cognitive Assessment; N = number of participants; NART, National Adult Reading Test IQ estimate; PD, Parkinson's disease; SSAI, Spielberger State Anxiety Inventory; STAI, Spielberger Trait Anxiety Inventory; AS, Apathy Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III (motor severity); H&Y, Hoehn and Yahr Score

Anxiety Inventory (STAI) (Spielberger et al. 1983), Starkstein Apathy Scale (AS) (Starkstein et al. 1992), and the National Adult Reading Test (NART) (Bright et al. 2002). In addition, participants were administered the Bond-Lader Visual Analog Mood Scales (Bond and Lader 1974) and the Spielberger State Anxiety Inventory (SSAI) (Spielberger et al. 1983) immediately prior to entering the MRI scanner. A motor severity laterality quotient was calculated for the left and right side by calculating the sum of the left lateralized motor severity and the sum of the right lateralized motor severity on the UPDRS-III scale, respectively. At the group level, there was no difference in the laterality of motor severity ($p > 0.50$).

Affective go-NoGo fMRI task

All participants performed the AGNG paradigm during fMRI. The AGNG paradigm utilized in this study used identical conditions to those previously described (Elliott et al. 2000, 2002a; Elliott et al. 2004), however the stimulus timings were modified to allow for slower motor response latencies associated with PD.

The AGNG task required patients to respond to words of a target valence (positive, negative or neutral), while simultaneously inhibiting responses to words of competing valence. Words of each emotional valence category: i) positive valence (e.g. 'triumph'), ii) negative valence (e.g. 'gloom') and iii) neutral valence (e.g. 'column'), were combined in six possible conditions of target and distractor valence category (see Table 2) in accordance with previous work (Elliott et al. 2000, 2002a; Elliott et al. 2004; Roiser et al. 2009). In addition, there were two orthographic control conditions in which neutral words were presented with the target and distractors being presented in either capital letters or lower case letters (see Table 2).

Participants were scanned while performing 24 task blocks interleaved with rest blocks. Immediately prior to the start of each task block the participant was presented with an on-screen instruction for 5 seconds stating which valence category to respond to (i.e. words belonging to the *target* valence category), and which not to respond to (words belonging to the *distractor* valence category). A 2000 ms period followed the instruction screen before the onset of stimulus presentation. In each block, words from two different emotional valence categories (either positive, negative or neutral) were presented on screen, one at a time. Words were pseudo-randomized such that no more than three words from a

Table 2 Affective Go-NoGo paradigm conditions

Condition	Target word valence	Distractor word valence
1	Positive	Neutral
2	Negative	Neutral
3	Neutral	Positive
4	Neutral	Negative
5	Positive	Negative
6	Negative	Positive
7	Neutral (capitals)	Neutral (lower case)
8	Neutral (lower case)	Neutral (capitals)

There were six valence conditions (Conditions 1–6), and two orthographic conditions (Conditions 7 & 8). In the orthographic conditions neutral words were presented with the target and distractors being presented in either capital letters or lower case letters

particular valence category occurred in succession. In each block, a total of 16 words were presented, each word appeared for 1000 ms followed by a 1300 ms period before presentation of the following stimuli. Stimuli timing was based on previous reports (see Murphy et al. 1999; Elliott et al. 2000; Elliott et al. 2002b; Elliott et al. 2004; Roiser et al. 2008; Gopin et al. 2011; Roiser et al. 2012), however modified to allow for protracted motor latency expected in a cohort of Parkinson's disease patients (given that Parkinson's disease is characterzed by motor impairments including bradykinesia, akinesia and rigidity, as well as non-motor deficits in executive function). Following each task block there was a 20 second rest block during which time a fixation cross was presented on screen. The fMRI paradigm was conducted in two runs, each consisting of 12 min, with a 10 min rest interval between runs. Modified stimuli timing allowed satisfactory task performance in both healthy control and Parkinson disease groups in this study.

All participants responded to stimuli using a button-box with their right hand (with the exception of one patient who responded using their left hand due to severe right-sided rigidity). Participants were instructed to respond to target stimuli as quickly and as accurately as possible. The paradigm was presented using *EPrime 2.0* software (Psychology Software Tools, Sharsburg, PA). Stimuli consisted of individual words were presented in black font (Times New Roman) on a white background.

Stimuli

In order to ensure that stimuli across each valence category were well matched for relevant linguistic variables, we generated a list of stimuli from previously published stimuli. Words with a positive or negative valence were selected from the Affective Norms for Emotional Words list (ANEW) (Bradley and Lang 1999). Words with neutral valence were selected from those provided by ANEW (Kousta et al. 2009) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) Affective Go-NoGo task. In total, 384 words were selected (96 positive valence, 96 negative valence, 192 neutral valence). Negative and positive valence categories were significantly different for valence (ANEW mean valence scores, $p < 0.001$) and were matched for arousal (ANEW mean arousal scores, $p = 0.159$). The three valence categories (positive, negative and neutral) were matched for word class ($p = 0.659$), frequency ($p = 0.970$), imagability ($p = 0.327$) and word length ($p = 0.189$).

Behavioral data analysis

Behavioral data were analyzed using SPSS 22. Behavioral reaction time (RT) data containing emotional valence (conditions 1–6) were analyzed using a repeated-measures ANOVA (*alpha* = 0.05). To investigate between-group differences for the orthographic conditions we compared RT across conditions 7 and 8 between the PD and healthy control groups using an independent samples t-test, *alpha* = 0.05. As there were no differences between conditions 7 and 8 (HC, $t = 1.098$, $p = 0.296$, $d = 0.448$; PD, $t = -1.966$, $p = 0.073$, $d = 0.120$; collapsed across groups: $t = 0.788$; $p = 0.435$; $d = 0.223$), we compared the mean RT collapsed across conditions 7 and 8 across groups for ease of interpretation. For blocks in which it was clear that participants had failed to attend to the task or had confused the targets and distractors (i.e. an error rate of greater than 30%), behavioral and BOLD data for that block were excluded from subsequent behavioral and imaging analyses. To ensure that the total percentage of behavioral errors in the included imaging data (blocks containing ≥ 4 errors) did not differ between groups we compared groups across each of the conditions using Mann-Whitney U Tests.

Image acquisition

Images were acquired on a General Electric 3 Tesla MRI (General Electric, Milwaukee, USA) with an 8-channel headcoil. T2*-weighted echo planar functional images were acquired in interleaved order with repetition time (TR) = 3 s, echo time (TE) = 32 ms, flip angle 90 degrees, 32 axial slices covering the whole brain, field of view (FOV) = 220 mm, inter-slice gap = 0.4 mm, and raw voxel size = 3.9 mm × 3.9 mm × 4 mm thick. 3D T1-weighted images were also acquired (TE 2.7 ms, TR 7.16 ms, inversion time (TI) 450 ms, 12 degree flip angle), with 196 slice phase encoding directions, orientated in the sagittal plane, with a resolution of $1 \times 1 \times 1.5$ mm^3.

Image processing

Statistical parametric mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/) was used for image processing and analysis. The image time series were first realigned during spatial preprocessing using rigid body motion correction with INRIAlign (Freire et al. 2002). A mean image was generated from the realigned series, and coregistered to the T1-weighted image. The T1 image was then segmented and normalized to the standard Montreal Neurological Institute (MNI) atlas T1 weighted template. These transformations were applied to the realigned EPI time series. Normalized volumes ($3 \times 3 \times 3$ mm^3) were then spatially smoothed using an 8 mm full-width half-maximum Gaussian kernel. The DARTEL toolbox (Ashburner 2007) was then used to create a customized group template from the segmented grey and white matter images and individual flow fields were used to normalize the realigned EPI volumes to the Montreal Neurologic Institute (MNI) atlas T1 template.

Whole-brain imaging analysis

First-level analysis was performed at the single participant level where individual contrasts maps were created in a general linear model by contrasting different emotional conditions. The general linear model included six motion and nuisance parameters, accounting for movement artifacts occurring in three directions of translation and three axes of rotation for each run. At the second level, we examined two contrasts of interest: i) group (2: PD, HC) × valence (2: positive target valence, negative target valence) factorial analysis, and ii) a between group independent samples t-test with emotional targets compared to neutral targets. For the 2 × 2 factorial analysis, regions showing significant main effects or interactions were identified using a group (2: PD, HC) × valence (2: positive target valence, negative target valence) factorial random-effects analysis. For this factorial analysis the valency of the target was modeled (positive or negative) with the neutral target used as first level baseline. In addition to the factorial analysis, we also examined group differences when processing emotional target words (collapsed across valence category: conditions 5 & 6, see Table 2) compared to neutral target words (conditions 3 & 4, see Table 2). At the whole-brain level we employed a statistical height threshold of $p < 0.001$ uncorrected, with a Bonferroni cluster threshold of FWE ($p < 0.05$) for multiple comparisons (calculated in SPM12).

Region of interest analysis

Given our strong a priori hypotheses regarding subcortical dysfunction during emotional processing in PD (LeDoux 2000; Moore 2003; Phillips et al. 2003; Postuma and Dagher 2006; Drevets et al. 2008; Korgaonkar et al. 2014), we conducted additional ROI analyses based on pre-specified neural regions (see Supplementary Fig. 1). The coordinates of each ROI were defined a priori, and thus independently, from the whole brain analyses using coordinates defined in previous work. Spherical regions of interest were constructed using the MarsBar toolbox in SPM 12 (Brett et al. 2002). MNI coordinates for the dorsal caudate (+/−11, 14, 9) were based upon a standardized caudate mask normalized to EPI-template space (Prodoehl et al. 2008), an approach previously utilized examine caudate activity in Parkinson's disease (see Shine et al. 2013). As the ventral striatum was not examined by Prodoehl et al. (2008), MNI coordinates for the ventral striatum (+/−9, 9, −8) were taken from a seminal resting-state fMRI study in which ventral striatum demonstrates strong connectivity with limbic cortical regions (Di Martino et al. 2008). Finally, given the structural and functional heterogeneity of the amygdalar complex (Swanson and Petrovich 1998), we defined amygdala MNI coordinates based upon results of work utilizing a conceptually similar affective decision-making paradigm (+/−22, −6, −16), in which amygdala activation was observed during an emotional face-matching paradigm requiring sensorimotor decisions based on emotional valence (Rhodes et al. 2007). Values for each ROI were then extracted and subsequently exported into SPSS 22 for two by two repeated-measures ANOVA, with the AGNG conditions as the within-subjects factor and group as the between-subjects factor.

Note that two of the patients with PD had a past history of a depressive disorder, but importantly, there was no evidence of current clinically significant levels of depression, apathy, anxiety or impulsivity in any patient involved in the study. To ensure that a past history of depression did not significant affect the major imaging results in this study we replicated the analysis following exclusion of these two participants (see Supplementary Materials).

Results

Demographic results

Results of the clinical and neuropsychological assessment are given in Table 1. The PD and healthy control groups were well-matched across a wide range of demographic and clinical variables including; age, education, MoCA, verbal fluency (both semantic category and letter fluency), mood, and for symptoms of depression, anxiety and apathy, however they were not matched for gender balance (Table 1).

Behavioral results

Table 3 shows the reaction time (RT), and % errors for the control subjects and PD patients during performance of the AGNG paradigm. Behavioral RT analyses were conducted on correct 'Go' trials (mean correct RTs are shown in Table 3 as a function of condition and group). Analysis of RT data for conditions containing emotional valence (condition 1–6) revealed no significant main effects for group ($F_{5,22}$ = 0.325, p = 0.575, η_p^2 = 0.014) or group × valence interactions ($F_{5,22}$ = 0.109, p = 0.745, η_p^2 = 0.005), however there was a significant main effect for valence ($F_{5,22}$ = 46.054, $p < 0.001$, η_p^2 = 0.677).

Post hoc pair-wise comparisons were conducted to explore the main effect for valence (see Supplementary Fig. 2). Condition 3 (neutral target, positive distractor) and Condition 4 (neutral target, negative distractor), were associated with significantly greater reaction time when compared to Condition 1 (positive target, neutral distractor), Condition 2 (negative target, neutral distractor), Condition 5 (positive target, negative distractor) and Condition 6 (negative target, positive distractor). There were no between-group differences for RT for the orthographic condition ($p > 0.05$). In addition, Mann-Whitney U Tests revealed that there were no significant between-group differences in % total error, % omission error (failed to respond to target), or % commission error (responded to distractor) for any of the conditions ($p > 0.05$ for all comparisons).

Functional imaging results

2 × 2 Factorial Analysis: Group × Target Valence

Significant group × valence interactions were observed in the left ventral striatum ($F_{1,23}$ = 4.842, p = 0.038, η_p^2 = 0.174), right ventral striatum ($F_{1,23}$ = 4.290, p = 0.050, η_p^2 = 0.158) and right amygdala ($F_{1,23}$ = 6.024, p = 0.022, η_p^2 = 0.207) in the ROI analysis. Whole-brain analysis revealed a significant main effect for group within the left superior temporal gyrus (−51, −31, 10), whereby the PD group showed reduced activation compared to healthy controls (Figs. 1 and 2, Table 4).

These results were broadly similar following exclusion of two PD patients with a past history of depression. Specifically, we observed significant group × valence interactions in the right amygdala ($F_{1,21}$ = 9.925, p = 0.005) and approaching statistical significance in the left ventral striatum ($F_{1,21}$ = 3.795, p = 0.065) and right ventral striatum ($F_{1,21}$ = 3.932, p = 0.061; see Supplementary Materials). At the whole brain level, the significant main effect for group in the left superior temporal gyrus failed to reach significance following exclusion of two PD patients with past history of depression (see Supplementary Materials).

T-test: Emotional Targets vs. Neutral Targets

The PD group revealed reduced activation in the left medial frontal gyrus (Brodmann area 10) (−9, 56, 10), for the contrast comparing emotional targets (collapsed across emotional

Table 3 Behavioral Results

Condition	Group	Reaction time Mean (SD)	Percentage Error, Mean (SD)		
			% Total Errors	% Commission Errors	% Omission Errors
Condition 1	HC	790.16 (100.2)	7.29 (5.7)	2.43 (2.5)	4.86 (3.2)
Positive targets, neutral distractors	PD	800.24 (116.9)	8.81 (6.7)	2.56 (2.3)	6.25 (4.4)
Condition 2	HC	768.66 (73.0)	3.65 (4.2)	1.13 (1.1)	2.52 (3.0)
Negative targets, neutral distractors	PD	807.94 (157.5)	4.49 (5.3)	1.28 (1.8)	3.21 (3.5)
Condition 3	HC	851.91 (69.3)	13.80 (9.5)	6.60 (4.0)	7.20 (5.5)
Neutral targets, positive distractors	PD	876.43 (156.3)	14.21 (7.8)	9.66 (4.2)	4.55 (3.6)
Condition 4	HC	869.22 (97.8)	7.77 (8.4)	1.52 (2.1)	6.25 (6.3)
Neutral targets, negative distractors	PD	872.88 (126.7)	9.99 (9.1)	4.17 (3.7)	5.82 (5.4)
Condition 5	HC	755.35 (84.1)	3.82 (4.6)	0.52 (1.3)	3.30 (3.3)
Positive targets, negative distractors	PD	780.64 (137.0)	4.97 (4.6)	0.32 (0.8)	4.65 (3.8)
Condition 6	HC	742.05 (89.1)	1.21 (2.9)	0.69 (1.0)	0.52 (0.9)
Negative targets, positive distractors	PD	788.99 (156.5)	3.44 (6.7)	1.04 (1.5)	2.40 (5.2)
Condition 7	HC	529.87 (55.7)	0.34 (1.2)	0.17 (0.6)	0.17 (0.6)
Neutral targets (caps), neutral distractors (lower)	PD	571.54 (112.4)	0.64 (1.6)	0.64 (1.6)	0.00 (0.0)
Condition 8	HC	552.67 (45.4)	0.52 (0.94)	0.52 (0.9)	0.00 (0.0)
Neutral targets (lower), neutral distractors (caps)	PD	584.90 (110.9)	0.96 (2.39)	0.80 (1.8)	0.16 (0.6)

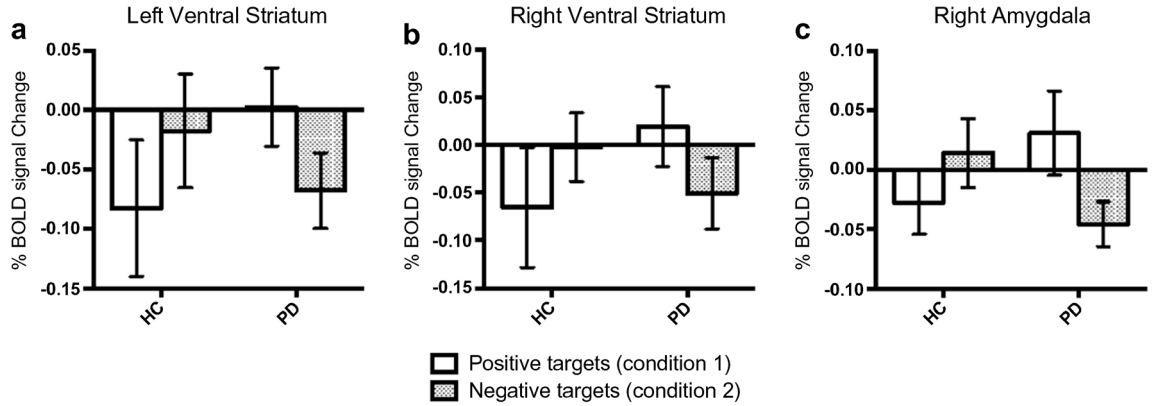

Fig. 1 Region of interest (ROI) results for positive compared with negative targets. Histogram representing the mean percent (%) BOLD signal change within a priori regions of interest (ROIs) that demonstrated significant group × valence interactions. Error bars represent SEM. *Abbreviations:* BOLD, Blood Oxygen Level Dependent; HC, Healthy Controls; PD, Parkinson's disease

valence) to neutral targets at the whole-brain level (Table 4). There were no regions that demonstrated greater activation in the PD group relative to controls. There were no significant group differences within the a priori ROIs. These results replicated following exclusion of two PD patients with a past history of depression (see Supplementary Materials). No cluster reached significance following correction for multiple comparisons for *within*-group whole-brain analysis for emotional relative to neutral targets in the HC and PD groups.

Discussion

We examined emotional word processing in PD using an AGNG paradigm in combination with fMRI. Our findings suggest that the pathology of PD alters the processing of emotional *valence* within subcortical limbic structures. Specifically, we found significant group × valence interactions in the ventral striatum and amygdala in response to words of differing emotional valence. These subcortical structures are of particular interest as they have been implicated in affective processing (LeDoux 2000; Phillips et al. 2003; Postuma and Dagher 2006; Arsalidou et al. 2013; Sieger et al. 2015), have been linked to affective processing deficits in mood disorders (Phillips et al. 2003; Drevets et al. 2008; Korgaonkar et al. 2014), and are modulated by ascending signals from the dopaminergic midbrain – the major focus of PD pathology (Braak et al. 2003).

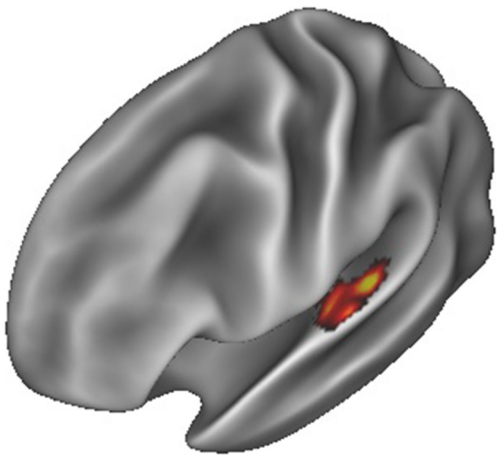

Fig. 2 Whole-brain results for the 2 × 2 Factorial Analysis: Group × Target Valence (Main effect of Group). The PD group demonstrated significantly reduced activation in the left superior temporal gyrus compared to healthy controls for the *positive – negative target* contrast. FWE $p < 0.05$

Top-down inhibitory control signals modulate activity in limbic circuits (Ochsner and Gross 2005), and abnormal inhibitory control signals have been linked to the pathogenesis of mood disorders in psychiatric populations (Murphy et al. 1999; Elliott et al. 2002a; Elliott et al. 2004; Erickson et al. 2005; Roiser et al. 2009; Kilford et al. 2015). Furthermore, recent work has suggested that abnormal cognitive control of affective processing may represent trait vulnerability to mood disorders (Hayward et al. 2005; Chan et al. 2007; Haas et al. 2007; Kilford et al. 2015). In this study, we have shown that non-depressed patients with PD demonstrate abnormal activation of specific subcortical structures during emotional word processing (Fig. 1). These findings add to a growing recognition that non-depressed patients with PD demonstrate impairments in affective processing and emotional regulation – and that these impairments can be observed at both a behavioral and neural level (see Peron et al. 2012 for comprehensive review). In light of recent work suggesting that impaired cognitive control of emotion represents trait vulnerability to mood disorders (Hayward et al. 2005; Chan et al. 2007; Haas et al. 2007; Kilford et al. 2015), our findings suggest a possible contribution of subcortical limbic circuit dysfunction in the pathogenesis of clinical mood disorders in PD. Future work is needed to further disentangle the interrelationship between Parkinsonian neuropathology, deficits in affective processing and vulnerability to clinical mood disorders in PD.

Table 4 Whole brain Imaging Results

Whole brain imaging results			
Region	Coordinates	Cluster extent	Z-score
2 × 2 Factorial Analysis: Group × Target Valence (Main effect of Group)			
Left Superior Temporal Gyrus	−51, −31, 10	62	4.36
T-Test Emotional Targets vs Neutral Targets			
Left *Medial Frontal* Gyrus	−9, 56, 10	69	4.54

The role of the amygdala in the generation and modulation of emotion is well established (LeDoux 2000). Post-mortem examination has revealed significant pathology within the amygdala in PD, including Lewy body pathology (Braak et al. 1994), reduced neuron density (Harding et al. 2002), pre-synaptic axon pathology (Bertrand et al. 2003), and diminished dopamine transporter binding (Ouchi et al. 1999). Results from our study suggest that previously documented amygdala pathology (Braak et al. 1994; Ouchi et al. 1999; Harding et al. 2002; Bertrand et al. 2003) is accompanied by abnormal signals within the amygdala during affective processing in PD (Fig. 1*c*). This finding is aligned with the results of a previous fMRI study, which found that patients with PD showed reduced activation of the amygdala during the processing of angry and fearful faces, compared to healthy matched controls (Tessitore et al. 2002). Further evidence suggesting that amygdala dysfunction impairs emotional processing in PD comes from studies directly comparing PD patients with and without clinical depression. These studies have shown that PD depression is associated with impaired functional connectivity of the amygdala (Hu et al. 2015) and reduced dopamine and noradrenaline transporter binding within the amygdala (Remy et al. 2005), compared to non-depressed patients with PD.

We have also demonstrated abnormal activity in the bilateral ventral striatum in non-depressed patients with PD during processing of emotional word valence (Fig. 1*a,b*). The ventral striatum represents an important hub embedded within the reward network (Sesack and Grace 2010). The ventral striatum receives dopaminergic innervation from the ventral tegmental area (VTA), and these dopaminergic signals encode motivation and reward, in turn guiding emotional and cognitive behavior (Bromberg-Martin et al. 2010). Data from human and animal studies have implicated the reward circuit (Russo and Nestler 2013), and in particular the ventral striatum (Epstein et al. 2006; Pizzagalli et al. 2009; Robinson et al. 2012; Golden et al. 2013), in the pathogenesis of Major Depressive Disorder. Recently, atrophy of the nucleus accumbens has been documented in PD (Mavridis et al. 2011; O'Callaghan et al. 2013; Hanganu et al. 2014), however it remains unclear whether nucleus accumbens pathology plays a significant role in pathogenesis of mood disorders in the PD population. Furthermore, PD patients with depression appear to have reduced dopamine and noradrenaline binding in the ventral striatum, compared to non-depressed patients (Remy et al. 2005). The current study provides among the first evidence to suggest that dysfunction of the ventral striatum (encompassing the nucleus accumbens) accompany, and potentially underlie, aberrant valence processing in PD.

In this study, we demonstrated a significant main effect for group within the left superior temporal gyrus in the Group × Target factorial analysis. Reduced superior temporal gyrus activity in the PD group is consistent with previous reports of temporal lobe hypometabolism associated with cognitive impairment in Parkinson's disease (Hosokai et al. 2009; Tard et al. 2015; Tang et al. 2016). Finally, we also demonstrated reduced activation of the left medial frontal gyrus to emotional targets (collapsed across valence category) in PD compared to healthy controls. One interpretation of this finding may be that dopaminergic depletion of the Parkinsonian striatum impairs recruitment of fronto-striatal macrocircuits during affective decision-making. Future studies examining corticostriatal functional connectivity during emotional processing will help to elucidate the potential contribution of corticostriatal circuit dysfunction in affective disturbance in PD.

Limitations & future directions

Despite insights offered by this study, some important methodological limitations need to be considered. Firstly, the limited small sample size of this study should be considered when interpreting these findings. Indeed, low statistical power may explain an absence of significant subcortical activation observed at the whole-brain level of analysis. A second limitation was that PD patients were medicated with their normal anti-parkinsonian medications during the fMRI experiment; thus, it is not possible to disentangle the possible influence of exogenous medication on the results of this study. Experimental pharmacological manipulation of specific neuromodulators (Bell et al. 2015; Yang et al. 2016) provides an important avenue for clarifying the role of specific neurotransmitter systems in non-motor symptoms of PD. Another potential limitation was that two of the patients with PD had a

past history of a depressive disorder, but importantly, there was no evidence of current clinically significant levels of depression, apathy, anxiety or impulsivity in any patient involved in the study. Furthermore, in an additional supplementary analysis we demonstrated that exclusion of these two patients did not significantly alter the results of this study. In addition, although the groups were matched across a large number of demographic, neuropsychological and clinical variables, groups were not matched for gender, and therefore, the possible confound of between-group gender differences cannot be excluded. Future studies carefully controlling for gender differences are needed to exclude this possible confound. A final consideration is that, while these findings highlight important disease loci underlying affective disturbance in PD; local neuropathology is accompanied by a complex array of large-scale adaptive and maladaptive changes in distributed functional brain networks (Fornito et al. 2015). Future functional connectivity analyses of cortical (Sporns 2013), subcortical (Forstmann et al. 2016) and brainstem (Bianciardi et al. 2016) networks will help to further clarify the neurobiology of affective disturbance in PD.

Conclusion

In conclusion, we have shown that patients with PD demonstrate abnormal valence-specific activation of the ventral striatum and amygdala during inhibitory control of emotional word processing. These findings contribute to the broader understanding of the interface between affect and cognition in PD, and may provide insights into the mechanisms underlying vulnerability to depression in PD.

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Author contributions PTB, KLM, DAC conceptualized the study; PTB, JMS, SJGL, DAC collected the data; PTB, MG, KLM, DAC analyzed the data; PTB wrote the initial draft; PTB, MG, JMS, KLM, SJGL edited the manuscript.

Compliance with ethical standards

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Conflicts of interest PTB, MG, JMS, KM, SJGL, DAC declare that they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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